

FRESH AIR '98'

A LOOK AT FDA'S MEDICAL GAS REQUIREMENTS

I would like to thank you for giving me this opportunity to speak to you today on a very important subject, compressed medical gases (CMG) and FDA's requirements for the manufacture of medical gases.

Fresh Air '98' provides FDA's interpretation of how the current good manufacturing practice (CGMPs) regulations apply to the manufacturing, filling, transfilling, cascading, etc. of compressed medical gases. Please note that this presentation is not all-inclusive.

Before we get started, I would like to remind you that medical gases are considered prescription drugs and as such are required to be dispensed by prescription only. ***Each firm has a responsibility to determine what their product(s) is being used for, and if your consignee (i.e., not patients) is registered with FDA or licensed with the state, prior to selling them any medical grade product.***

Medical gases not filled in accordance with the current good manufacturing practice regulations can and have resulted in medical gases that are contaminated which can cause serious injury and/or death to patients administered the gas. In fact, injury and death of patients has occurred in the past due to CGMP problems.

Who exactly is required to register? Any person or firm filling liquid to liquid, liquid to gas, and/or gas to gas is considered a manufacturer and as such is required to register and list with the agency and to comply with the CGMPs. In addition, you should check with your state to determine if there are any state requirements, such as licensing.

Further, we are unaware of any schools of pharmacy or State Boards that offer education and/or training for the filling of CMG, therefore, any pharmacy involved in the manufacturing of medical gases would be required to register and list with the agency and will be inspected. However, a hospital pharmacy that provides oxygen for inpatient use only would not be required to register.

Presented by Duane Sylvia, Consumer Safety Officer, Center for Drug Evaluation and Research, Office of Compliance during the Detroit District Office's Medical Gas Workshop held on November 10, 1998, at South Bend, Indiana.

If you acquire or are in the process of purchasing a firm, it is your responsibility to know their CGMP history. All employees of the purchased firm should be knowledgeable of your corporate requirements, including but not limited to adequate training, written operating procedures, applying your label to the containers, etc.

What are the current good manufacturing practice regulations for medical gases? At the present time, there are no specific regulations for medical gases. However, the Commissioner realized the requirements in the more general CGMP regulations, i.e., 21 CFR 211 with certain stated exceptions, are applicable for medical gases.

In the preamble of the revised CGMP regulations issued September 29, 1978, the agency recognized that medical gases were different from the traditional dosage forms in many respects, such as reuse of the container closure systems, the product at each manufacturing stage is considered a finished drug product, and full testing occurs every time the product changes hands.

So based on the information gathered from 17 years of inspections of compressed medical gas firms and several meetings with the Compressed Gas Association (CGA), the first Compressed Medical Gases Guideline was issued in June of 1981, with a subsequent revision in 1983. In February of 1989, the guideline was revised to address the evolving home care area, or the delivery of liquid oxygen to patients at home. Currently, we are working with the industry and CGA on developing Fresh Air into the next official guidance document.

Let's briefly look at how FDA enforces the requirements and what our experience has been with the medical gases industry from a national standpoint.

FDA has the responsibility of enforcing the ***Federal Food, Drug, and Cosmetic Act (the Act)***. This law gives FDA the authority to conduct inspections, collect and analyze product samples to assure that foods, drugs, cosmetics, biologics, and medical devices are safe and meet the appropriate quality standards.

The Act states that a drug, such as medical oxygen, etc. is adulterated and subject to legal action if it is not manufactured in accordance with the CGMPs, or does not comply with appropriate official standards such as strength and quality as cited in the United States Pharmacopeia/National Formulary (U.S.P.).

According to the Act (section 501) a drug is deemed adulterated if the methods used in, or the facilities or controls used for, its manufacture, processing, packing, or holding do not conform to or are not operated or administered in conformity with current good manufacturing practices to assure that such drug meets the requirements of this Act as to safety and has the identity and strength, and meets the quality and purity characteristics, which it purports or is represented to possess.

Section 510 of the Act requires all drug manufacturers, including fillers of medical gases, to

REGISTER ANNUALLY with the agency and to list what products are produced, or filled. Failure to comply with this requirement is a violation of the law which can ultimately result in legal action.

Please note: One of the requirements for listing is that you submit an actual specimen of the finished label(s) you apply to the drug product(s). This would include high pressure cylinders and both large cryogenic vessels as well as cryogenic home vessels. If a firm is utilizing a small, grocery-store type sticker to apply an expiration date, and/or a lot number to the product, you must submit a specimen along with your label on the Form FDA2657.

Once a firm is registered, the FDA will automatically send the registration form back to you annually to verify the status of your operation. For registration and listing questions and to request the booklets and forms, contact the Product Information Management Branch @ (301)594-1086.

Finally, section 704 of the Act authorizes FDA to enter each facility to conduct an INSPECTION to assess compliance with the law. Failure to permit an inspection is a violation of the law, which can eventuate in legal action. Under this section, FDA has the authority to collect and review all records, except financial data records that relate to the manufacture of a drug.

FDA is required by statute to inspect each registered drug facility at least once every two years. Often, it is more frequently, especially where we suspect or know of a problem with a specific firm or the industry as a whole.

If an inspection determines that a firm is significantly deviating from the CGMPs and satisfactory corrections have not been initiated, FDA will initiate regulatory action intended to prompt a firm to correct its problems and protect the patient.

There are several courses of action we can take within the authority of the law, these include:

- issuance of a warning letter;
- seizure of a product, including storage tanks, high pressure cylinders, cryogenic home vessels on the premises, and trucks/vans containing the large cryogenic vessels;
- an injunction;
- prosecution;
- disapproval of government contracts; and
- informing the Health Care Finance Administration.

Let's look at the general state of compliance in the compressed medical gases industry today? We are finding that the general state of CGMP compliance is not very good. This is evident by the data contained in the next couple of slides which represents the total number of regulatory actions for the fiscal years of 1992 to 1997. In '92' - 112; in '93' - 117; in '94' - 91; in '95' - 109, in '96' - 103, and in '97' - 152. The next slide shows the seizure actions approved, 21 in '92', 12 in '93', 15

in '94', 11 in '95', 6 in '96', 7 in '97'. We also had one injunction and one prosecution.

This regulatory action rate indicates a need for the industry to improve its overall compliance with the CGMPs.

NOTE: In accordance with the Regulatory Procedures Manual - August 1997, Chapter 10, FDA is under no legal obligation to warn firms or individuals that they or their products are in violation of the law prior to taking formal regulatory action. If your firm has multiple locations, and if any one of these locations receives a warning letter for significant CGMP violation, an FDA483, etc., and the responsible persons have been advised, and if another inspection finds continuing violations of the nature reported in the prior warning, then FDA has the option to proceed immediately to a seizure or an injunction.

LIQUID TO LIQUID FILLING

(Pertains to the filling of cryogenic home vessels either a patient's home or onsite)

1. TESTING OF THE INCOMING LIQUID OXYGEN

If a firm dispenses liquid oxygen (LOX) from large cryogenic vessels into cryogenic home vessels, then one of the following procedures should be complied with:

Please note all of the conditions listed under each of the following testing scenarios must be met in order to satisfy that requirement.

- a) No testing would be required, as long as the receiving firm witnesses the testing, i.e., identity and strength of each large cryogenic vessel by the supplier, receives a valid COA for each vessel, and documents that the testing has been witnessed.

In addition: The employee responsible for witnessing the testing is required to receive training specific to the analytical methodology being witnessed, and this training should be documented and maintained on file.

- b) If the testing is not witnessed, then the receiving firm may rely on a valid COA for the strength determination, but should perform an identity test on **EACH** large cryogenic vessel received or filled by the supplier. The firm is required to periodically verify the reliability of the supplier's analysis which should be performed at least once a year by:

- 1) visiting the supplier to:

- determine if the supplier is registered with FDA;
- assure the supplier is following appropriate written testing

procedures;

- witness any analytical testing performed, including calibration of the analyzer; and
- documentation that the above was performed, or

2) by taking a sample from a recent delivery to a third party for analysis for conformance with U.S.P. specifications.

c) If a firm fails to comply with any of the conditions outlined above, then full U.S.P. testing would be required to be performed on the incoming drug product, i.e., each large cryogenic vessel.

2. TESTING OF A STORAGE TANK

-under this scenario, a firm usually rents or leases a storage tank which is located on their premises and then fills either vehicle mounted vessels which in turn are used to fill cryogenic home vessels at a patient's home or fills CHVs on site.

An identity and strength test should be taken directly from the storage tank after each oxygen delivery, prior to the filling of any cryogenic vessels including cryogenic home vessels. Large cryogenic vessels filled from this storage tank need not be tested as long as:

- a) No other storage tank(s) is located on the premises;
- b) They are dedicated to the delivery of oxygen by the firm for home care use only;
- c) They have not been completely emptied or have not been out of service. [If the vessel is “liquid empty. i.e., without liquid oxygen” AND has a gaseous pressure below 15 psig, the vessel should be requalified for full U.S.P. testing]; and
- d) A valid certificate of analysis is received with each delivery, and maintained on file.

3. TESTING OF CRYOGENIC HOME VESSELS

The most significant condition in the filling of cryogenic home vessels is the control of the cryogenic home vessels. If the possibility exists that a contaminant or a foreign product could be introduced into the cryogenic home vessel, then the CGMPs require full U.S.P. testing of each vessel. Industry practice calls for the firm that owns the cryogenic home vessels to perform the filling and to not allow any other firm to fill these vessels.

a) No testing of the cryogenic home vessels would be required as long as all of the following criteria are met:

- 1) liquid oxygen is the only liquid being filled on the premises;

- 2) the incoming liquid oxygen is adequately tested according to one of the methods outlined under Items #1 and 2 (See above); and
 - 3) the cryogenic home vessels are filled by the firm.
- b) If any other liquid is being filled on site or if the incoming liquid oxygen is not tested in accordance with one of the methods outlined under Items #1 and 2, then **ALL** cryogenic home vessels filled are required to be tested for full U.S.P. specifications.
 - c) *If a home care company (HCC) has their cryogenic home vessels filled by a third party, then prior to delivery, the HCC is required to inspect each vessel to assure a correct label including a lot number has been applied by the filling firm, prior to release to the patient. In addition, the HCC should obtain a written letter of guarantee from the supplier describing the supplier's responsibility to perform all required prefill inspections, finished product testing, labeling, etc. and this guarantee should be updated annually.*

This concludes the testing requirements for the filling of cryogenic home vessels that are either filled on site and delivered to a patient's home, i.e., milk canning, etc. or are filled at a patient's home, i.e., curbside.

Combining a new shipment of drug into a storage tank, or any cryogenic vessel with the remainder of a previously received, tested, and approved lot causes the commingling of the material. The result is that the previously approved material becomes an integral part of an unapproved new lot and cannot be used until such lot is approved for use.

LIQUID TO GAS and FILLING LARGE CRYOGENIC VESSELS (Pertains to suppliers such as welding supply companies)

This operation involves the filling of high pressure cylinders via a heat exchanger or a vaporizer, and the filling of large cryogenic vessels. The testing requirement is immediately after each delivery, the commingled liquid oxygen should be tested for full U.S.P. specifications. This may be accomplished by:

- 1) taking a sample directly from the storage tank, or
- 2) testing a cylinder from the first filling sequence (manifold or rack) which is the most commonly seen practice.

A storage tank is only required to be tested prior to the filling of a medical product.

Under this scenario, **each and every** cryogenic vessel filled is required to be tested prior to release, since cryogenic vessels usually contain residual product and a commingling of new and old product results. This commingling produces a new batch and is required to be analyzed and assigned a new lot number.

NOTE: A valid certificate of analysis should be provided with each cryogenic vessel, and the COA should be maintained on file.

Next, let's discuss the specific CGMPs that a manufacturer of medical gases is expected to follow. A word of **CAUTION**, please check the accuracy of any information you may receive with FDA before changing or implementing a possible violative CGMP practice or procedure.

RESPONSIBILITY OF QUALITY CONTROL UNIT

Section 211.22(a)

Each firm is required to establish a quality control unit (QCU) that has the responsibility and authority to approve or reject all drug product containers, closures, in-process materials, labeling, written procedures, the authority to review production records to assure completeness and accuracy, and is responsible for the approval or rejection of all manufactured drug product. The responsibilities and procedures applicable to the QCU should be in writing and these procedures should be followed. Further, the designated person should meet the Personnel Qualifications requirements listed below.

A small firm may designate a single individual with the above responsibilities.

PERSONNEL QUALIFICATIONS

Section 211.25(a)

In any manufacturing operation involving human manipulation there are hazards which may be created by preoccupation, mental lapse, carelessness and the like. Therefore, all on-the-job and CGMP training should be revisited at frequent intervals and needs to be conducted by qualified individuals.

A firm is expected to establish detailed written procedures (training program) outlining the specific areas of the firm's operation to be covered. On-the-job training is acceptable, as long as the training is conducted by a qualified individual on a frequent basis. Any employee involved in the manufacturing, filling, processing, handling, holding, or shipping is required to be trained in both on-the-job and CGMP training. This would include all delivery and/or truck drivers who deliver medical drug products.

A word of caution, if you acquire a firm, prior to startup under your corporate name, all

employees should be trained under your written operating procedures.

The lack of CGMP training is one of the most overlooked areas observed at most medical gas firms. CGMP training should be conducted by qualified individuals on a continuing basis and with sufficient frequency to assure that employees remain familiar with the CGMP requirements that are applicable to their function. Conducting CGMP training once a year is not recommended, but instead should be presented in smaller more manageable portions, and presented throughout the year with documentation of the type, time, and attendance of each session.

All training should be documented.

Additional information may be obtained from:

- 1) the National Technical Information Service, (703)605-6050 to obtain a copy of the Compressed Medical Gases - CGMP Inspection videotape. This videotape covers the filling of high pressure cylinders only. Request AVA19784VNB1.
- 2) FDA websites where you may review and retrieve: 1) the quarterly publication entitled *The Human Drug CGMP Notes* that address policy questions and other pressing issues under the GAS WHAT? column, 2) Fresh Air '98' presentation, and 3) the CGMPs. To obtain an electronic version of these documents and previous editions, using the Internet type: **<http://www.fda.gov/cder/dmpq/cgmpnotes.htm>, or [gases.htm](http://www.fda.gov/cder/dmpq/gases.htm), or [cgmpregs.htm](http://www.fda.gov/cder/dmpq/cgmpregs.htm), respectively.**
- 3) the Superintendent of Documents at (202)783-3238 for a copy of Title 21, Code of Federal Regulations, Parts 200 - 299.
- 4) your supplier who may be offering CGMP training and other types of training for their consignees throughout the year.
- 5) the Compressed Gas Association at (703)412-0900 for their educational pamphlets, bulletins, and videos, or the National Welding Supply Association at (215)564-3484.

DESIGN AND CONSTRUCTION

Section 211.42

Any building, van, truck, etc. used in the manufacture, processing, holding, or delivery of a medical gas should be of suitable size and design. There should be adequate space for the orderly placement of equipment and materials to prevent mixups and contamination.

Quarantine areas should be set up to separate the incoming drug product, cylinders and vessels, equipment, and the finished product prior to release. *This is especially true for trucks that make*

both medical and industrial deliveries.

EQUIPMENT CLEANING AND MAINTENANCE

Sections 211.67(a)

All equipment used in the manufacturing of a drug product shall be cleaned, maintained, and sanitized at appropriate intervals to prevent contamination that would alter the safety, identity, strength, quality, or purity of the drug.

The Commissioner intended that containers and closures be clean before use. In some instances this will require the manufacturer to perform separate, and sometimes extensive, cleaning cycles. In other instances it may not be necessary for the manufacturer to undertake a specific cleaning operation. A word of caution, equipment used to supply industrial product is required to be cleaned, and qualified before being used with medical products.

If the possibility exists that a medical product, equipment, or containers or closures may have been exposed to a contaminant(s), then a test for that contaminant(s) is required. The U.S.P. General Notices, Foreign Substances and Impurities section states it is manifestly impossible to include in each monograph a test for every impurity, contaminant, or adulterant that might be present. Therefore, the U.S.P. monograph is not a total impurities screen. In fact, your testing procedures should address all possible contaminants your equipment may encounter, including high pressure cylinders and cryogenic vessels.

EQUIPMENT CALIBRATION

Section 211.68

A firm should establish written procedures addressing a calibration schedule for all equipment used during its operations. A firm may reference in the written procedures the manufacturer's instruction manual for the recommended calibration schedule, as long as the manual is available and is followed to assure proper functioning of all equipment. This would include pressure gauges, vacuum gauges, thermometers, scales, etc.

Vacuum gauges are required to undergo two (2) calibrations. The first calibration which is performed on a daily basis with no vacuum present, is a check to assure that the needle on the gauge returns to "zero." This daily check should be recorded on the batch production record or a separate log. The second and more significant calibration requires the vacuum gauge to be calibrated to standards established by the National Institute of Standards and Technology. The frequency of calibration should be the manufacturer's requirements, or if no schedule exists then a twice a year cycle would be acceptable, or a firm could establish their own calibration schedule from their historical data.

Likewise, thermometers are required to be calibrated in accordance with the manufacturer. We have allowed firms to store under lock and key, a thermometer similar to the ones in use in the filling area, and to periodically compare the stored thermometer to the thermometers used during filling. This calibration is required to be documented in a separate log.

In the September 1994, edition of the Human Drug CGMP Notes, we informed the industry of recent problems encountered by the use of check valves in their supply systems to prevent the back flow of foreign or contamination into the lines. It has been our experience that these check valves can be compromised where a proper seal does not occur. Therefore, prior to use of a check valve, a firm must perform a validation study to assure they are acceptable for use. A recent recall involved the contamination of high pressure cylinders with oxygen compatible oil which contaminated the system following a vacuum pump explosion which forced the oil past the check valve.

COMPUTER SYSTEMS VALIDATION

All computer systems are required to be validated. Before a firm converts any of its manual operations to an automated operation that will be controlled by a computer system and associated software, it is required to validate the computer system and associated software.

What exactly is validation? Well, according to the Guideline on General Principles of Process Validation, May 1987, validation is defined as establishing documented evidence which provides a high degree of assurance a specific process will consistently produce a product meeting its pre-determined specifications and quality attributes.

Computer Validation references:

Good Computer Validation Practices - Common Sense Implementation by Teri Stokes, Ronald C. Branning, Kenneth G. Chapman, Heinrich Hambloch, and Anthony J. Trill, Interpharm Press, Inc. (708)459-8480

PDA Journal of Pharmaceutical Science and Technology, Technical Report #18, 1995, Volume 49, Number S1, Validation of Computer-Related Systems.

Pharmaceutical Engineering, July/August 1995, Computer Systems Validation: A Historical Perspective by Dr. Guy Wingate.

Pharmaceutical Technology, March, April & May 1992, GMP Documentation Requirements for Automated Systems: Part I, II, & III, respectively.

Drug product containers and closures play a critical role in assuring that the patient is provided a drug product of essentially the same strength, quality, and purity.

The CMG industry is the only industry allowed to reuse the drug product containers and closures. Therefore, high pressure cylinders and all cryogenic vessels are required to undergo strict prefill inspections, prior to filling with a medical gas. Medical gases cylinders are prepared under carefully controlled and strict inspections.

Recently, we have received several injury reports pertaining to high pressure cylinders contaminated with unusual chemicals, such as freon 14, benzene, chlorine, etc. All high pressure cylinders are required to be cleaned, prior to the introduction of a medical gas. Adequate cleaning procedures should be established and followed in order to prevent any contamination or impurities from being introduced into a medical drug container. The agency is currently investigating the possibility of requiring dedicated medical drug containers, similar to the requirements of the European Community.

Prefill Inspections

1. High Pressure Cylinders

Under the CGMPs, a firm is required to perform the following inspections on each and every cylinder:

- **hydrostatic testing date [cylinder markings]** - Steel cylinders are tested every five (5) years, unless a "*" follows the testing date which means the cylinder may be tested every ten (10) years. Aluminum cylinders must undergo testing every five (5) years.

The Department of Transportation has renewed Exemption E-10922 to Ultra Test Corporation, Division of FIBA Leasing authorizing the use of one hundred percent ultrasonic inspection of steel high pressure cylinders in lieu of the internal visual and hydrostatic retest.

- an **external examination** of all cylinders looking for dents, arc burns, dings, oil, grease, and other signs of external damage that might cause a cylinder to be unacceptable or unsafe for use.

A visual inspection for any fire or thermal damage is required.

- **venting or blowing down** to atmospheric pressure if any gas is present; or inverted and drained if it contains a liquid.

- an **odor or sniff test** performed during the venting of a cylinder to detect the presence of a foreign gas or odor. (This test must not be performed on carbon dioxide, nitrous oxide, or anesthetic gases.)
- a **hammer test** which is a valuable indicator of internal corrosion, should be performed on empty unpressurized cylinders with a 10 year retest date. [Cylinders with a 5 year test date are not required to undergo a hammer test.] The hammer test consists of tapping the cylinder sidewall with a light blow using a ball-peen hammer, etc. A good cylinder will make a clear bell-like ring, while a dull ring would indicate internal corrosion. All cylinders with a dull ring should be marked as unacceptable and quarantined.

This procedure must not be performed on aluminum cylinders.

- the **valve assembly** should be examined for the presence of debris, oil or grease which should be removed before use, and for the correct CGA valve which is unique for the specific medical gas. Recent problems encountered with valve assemblies has necessitated stricter inspections:
 - are the inlet threads or outlet threads damaged?
 - is the handwheel or valve stem bent?
 - are there noticeable signs of damage?
 - are there visible signs of corrosion inside the valve?
 - are there visible signs of excessive heat or fire damage?
- **the correct color** for the corresponding medical gas. The medical gas industry has adopted a color code system to aid in the identification of medical gas cylinders. A firm should not rely solely on the color coding for identification of the medical gas to be filled. What a firm should rely on is the drug product label, the specific valve for the medical gas, and then the color.
- the **label**. Old labels need not be removed if they are identical to the labels currently used, are in good condition and are applicable to the product being filled. However, obsolete labels or labels containing old lot numbers should be removed. A firm may not apply another label on top of an old label.
- **vacuum evacuation** of each cylinder by means of a vacuum pump capable of pulling a vacuum of at least 25 inches of mercury at sea level before oxygen or any other medical gas is introduced into the filling manifold. [See attached Altitude Pressure chart.]

Cylinders failing any of these prefill inspections are required to be quarantined to a separate area

to prevent their use in the filling process.

All of the above high pressure prefill inspections are required to be documented on a batch production record under the appropriate headings.

2. Cryogenic home vessels

Cryogenic home vessels are required to undergo certain prefill inspections, prior to filling. The required prefill inspections are usually contained in the manufacturer's manual supplied with each cryogenic vessel. At a minimum there should be:

- an external vessel inspection,
- ***all inlet and outlet connection inspection,***
- a volume or contents gauge inspection, and
- a label inspection. The firm filling these vessels must apply a drug label.

Documentation that each cryogenic home vessel has undergone the above inspections should be entered on a cryogenic home vessel batch production record under the appropriate headings.

3. Large cryogenic vessels

Large cryogenic vessels are required to undergo specific prefill inspections, prior to filling. At a minimum there should be:

- an external vessel inspection,
- ***all inlet and outlet connection inspection,***
- a volume or contents gauge inspection,
- an inspection for the DOT markings,
- an inspection to ensure that the pressure relief device on the unit is appropriate for its intended use, and
- a label inspection. The firm filling these vessels must apply a drug label.

In the past 2 years, we have received several reports of deaths and serious injuries following the installation of an industrial grade product included with the delivery of Oxygen U.S.P. to hospitals. Subsequently, the industrial vessels outlet fittings were replaced with an oxygen fitting allowing the industrial product to be connected to the hospitals oxygen system.

In order to prevent this from occurring in the future, FDA is implementing the following improvements to all large cryogenic vessels:

- should be dedicated to medical use only;***
- should have permanently brazened fitting or connection in place, i.e., both the inlet and outlet; or utilize a tamper-evident device on each fitting or connection, and***
- on the dome there should be a medical product designation, i.e., Oxygen U.S.P. under***

the fittings or connections, or apply a 360 degree wrap around tape at the top of the vessel.

FILLING OPERATION

The two most common methods of filling high pressure cylinders are:

- a) Liquid to Gas. Liquid oxygen is pumped from a storage tank through a vaporizer or heat exchanger converting the liquid into a gas which travels through piping. Attached will be a filling manifold usually with multiple outlets to which the high pressure cylinders are attached to be filled; and
- b) Gas to Gas, commonly referred to as cascading [See Definition #4].

During the filling operation, the filler is required to perform a **heat of compression** check which is accomplished by lightly touching the exterior of each cylinder undergoing filling. A warm cylinder indicates the cylinder is filling properly, while a cool or cold cylinder may not be filling properly and should be investigated and addressed.

CHARGE-IN COMPONENTS **Section 211.101a**

Each batch shall be formulated with the intent to provide at least 100 percent of the labeled medical product; therefore, each cylinder should be filled to its indicated service pressure or to the indicated net content statement listed on the label.

Temperature & Pressure [Boyle's Law]

Because of the characteristics of gases in a closed container, such as a high pressure cylinder, to increase in pressure with rising temperature the possibility exists that a cylinder filled at a safe pressure at room temperature could reach a dangerously high pressure at elevated temperatures. Therefore, this increase in the pressure needs to be compensated for to ensure that the cylinder's service pressure is not exceeded, but is filled to the stamped service pressure.

Since heat and pressure are directly proportional a temperature pressure chart [See attached chart] is used to adjust the filling pressure so that the service pressure will not be exceeded at 70°F. The filling temperature is determined by attaching a thermometer to the side of one of the cylinders attached to the manifold during filling, including aluminum cylinders.

Prior to shutting off the gas flow via the valves, the temperature and filled pressure reading is required to be recorded on the batch production record under the temperature pressure column.

NOTE: According to the Department of Transportation, Title 49 CFR 173.302(e): Verification of container pressure. Each day, the pressure in a container representative of that day's compression must be checked by the charging plant after the container has cooled to a settled temperature and a record of this test kept for at least 30 days. This requirement should not be confused with the above FDA's temperature and pressure requirement.

If a "+" symbol follows the hydrostatic testing date, then that cylinder qualifies for a ten percent (10%) overfill unless the valve is equipped with a fusible, metal-backed safety. These are usually found on post valves for gaseous fills only. Aluminum cylinders must not be overfilled.

Valve Leak Testing

During the filling operation, the first of the two required valve leak tests should be performed. At this time, each cylinder valve is tested for valve packing leaks, safety plug leaks and other valve leaks using a leak detecting solution, such as Sherlock Leak Check. The valve packing leak test is required to be performed with the cylinder under pressure and while the cylinder valve is opened.

Routinely, a leak detection solution is sprayed on and around the entire valve assembly, looking for bubbles indicating a leak. This solution should be oxygen compatible and should not contain hydrocarbons. Solutions containing soap are not recommended since they may be corrosive to the valve stem and may develop a residue buildup.

RETESTING OF CONTAINERS

Section 211.87

Containers and closures are required to be retested for identity, strength, quality, and purity and approved or rejected by the quality control unit, after exposure to conditions that might adversely affect the component, drug product container or closure.

This would pertain to any container or closure used for industrial products, any new cryogenic home vessels or any portable unit.

If a cryogenic home vessel is repaired or if maintenance is required, then upon return and after filling, the vessel should at the least be retested for identification, prior to redistribution.

WRITTEN PROCEDURES

Section 211.100(a & b)

There cannot be different standards of quality of drug products for large and small manufacturers. Written procedures are appropriate regardless of the size or complexity of the operation. They provide a basis for the uniform performance of a function, and they provide a step-by-step

description on how to perform a specific task, function, or operation.

Medical gas manufacturers are expected to establish and follow detailed written procedures covering all aspects of their operation. These procedures should cover establishing a quality control unit, training, prefill, fill and post fill operations, analytical testing, labeling, calibration and maintenance of equipment, distribution, recall, complaint files, etc.

In addition, it does little good to enact new procedures and controls if they are not read, understood, and followed by all employees. All written procedures are required to be reviewed, approved, signed, and dated by the quality control unit.

CALCULATION OF YIELD **Section 211.103 & 184(c)**

At the current time, we are not enforcing the calculation of actual yields and percentages of the theoretical yield as required by Section 211.103 and from the 211.184(c) requirement that records should include an individual inventory record of each component, and a reconciliation of the use of each lot of component.

PACKAGING AND LABELING CONTROL **Sections 211.122, 125, & 130**

A firm should establish written labeling procedures covering the receipt, identification, storage, handling and examination of all labeling. Procedures should be established for the reconciliation, issuance, returns, and security of labeling. There should be written procedures to assure that the correct label is used on the drug product including the identification of each batch with a lot number.

All high pressure cylinders, large cryogenic vessels and cryogenic home vessels are required to bear an adequate drug label. This label is usually the responsibility of the manufacturer, filler, transfiller, etc.

NOTE: There should be only one drug label on a high pressure cylinder or cryogenic vessel, and that label is usually applied by the manufacturer, filler, transfiller, etc. of the drug product. Cryogenic home vessels come from the manufacturer with a DEVICE label, which should not be confused with the required drug label. Further, the device label must not be removed.

Upon receipt from the printer, all labels should be counted to assure the quantity of labels received matches the quantity of labels ordered, and they should be examined and compared against the master label to assure correctness.

If a firm uses a small, grocery-store type sticker to contain an expiration date or a lot number, these are required to be covered in your written procedures. Further, these stickers should not fall off.

Section 503 of the Act requires prescription drugs to bear the statement: "Rx Only or ~~R~~Only."

However, if a firm sells Oxygen U.S.P. to emergency medical services, i.e., fire departments, rescue squads, ambulance companies, etc. or for emergency use, then the label is required to contain the statement: **"For emergency use only when administered by properly trained personnel for oxygen deficiency and resuscitation. For all other medical applications, Rx Only."**

[A firm may continue to use the old statement, "Caution: Federal law prohibits dispensing without prescription" on its label and still be in compliance. However, at the next printing of labels or no later than February 19, 2003, the new "Rx Only" statement must be used instead of the old federal caution statement.]

LOT NUMBERS

According to the CGMPs, each manifold filling sequence, each uninterrupted filling sequence, each cryogenic vessel filled, and each storage tank following a delivery is considered a new lot and is required to be assigned a new lot number.

The assigning of a single lot number for an entire days production is not acceptable. A manufacturing operation, such as the filling of high pressure cylinders on a multi-outlet manifold, is governed by a set of manufacturing procedures or conditions which when performed from the beginning to the end of a process provides assurance that the batch is uniform and consistent. As such, each batch is in itself a separate entity with its filling operations unique to that filling sequence.

For firms filling liquid oxygen only for home patient delivery, each of the large cryogenic vessels or dewars placed or permanently mounted in a van or a truck are required to be assigned a unique lot number.

At the present time, cryogenic home vessels filled at a patient's home, i.e., curbside, are not required to bear a lot number. However, cryogenic home vessels filled on site and stored for future delivery, or cryogenic home vessels filled by a third party, require lot numbers.

Label removal on aluminum cylinders may be accomplished by carefully removing the label with an acceptable scraper, etc. Caution should be exercised if using any sharp object, files, razor blades, etc. so as to not cause damage to the cylinder walls and render the cylinder unacceptable.

EXPIRATION DATING AND STABILITY TESTING
Sections 211.137 & 166

The Compressed Gas Association submitted a citizens petition to exempt medical gases from compliance with the expiration dating requirements of 21 CFR 211.137. A final decision has not been reached, in the interim, we are not requiring that firms apply expiration dates to the labels of medical gases. However, if a firm's written procedures call for an expiration date, then we would expect you to be following these procedures and apply an expiration date to the product.

Medical gases or medical gas mixtures that are considered new drugs or investigational new drugs are required to undergo stability testing in order to determine an expiration date.

HOLDING & DISTRIBUTION
Sections 211.142 & 150

Section 211.142 states written procedures should be established describing the warehousing of the drug product, especially the quarantining of the finished drug product, prior to release.

Section 211.150 states there should be written procedures describing a system by which the distribution of each lot of drug product can be readily recalled.

Please note that reliance on a system of contacting every customer in case of recall is not sound. Under this type of system recalls could be delayed if customers who received recalled products were not contacted because they were not customers at the time of initiation of the recall. Conversely, customers who never received the product could be contacted, thus taxing the resources of the firm and FDA. A blanket recall might also cause unneeded patient anxiety, and the Commissioner does not believe that the same accountability for each lot is inherent in a system that relies on contacting every customer.

LABORATORY CONTROLS
Sections 211.160(a) & 160(b)(4)

Section 211.160(a) - Written procedures covering any specifications, standards, sampling plans, and testing should be established and followed to assure that each batch of drug product conforms to final specifications.

A firm should describe how many cylinders or cryogenic vessels are to be tested, when that testing is to occur, the acceptance criteria, and the course of action to be taken if test results fall outside of established specifications. This is especially significant for firms filling high pressure cylinders one at a time.

Section 211.160(b)(4) - Oxygen analyzers, instruments, gauges, etc. should be calibrated at suitable intervals in accordance with the manufacturer's instructions.

CALIBRATION STANDARDS

Calibration standards should be accompanied by a certificate of analysis certifying the actual test results for the standard, and are required to be primary standards. Calibration standards cannot be medical grade or industrial grade, and should be obtained from a manufacturer of standard gases.

COA - Calibration Standards

Each COA for a calibration standards is specific for that particular cylinder, and should provide the following information:

- 1) Supplier's name and complete address
- 2) Name of the Product (Cannot be medical or industrial grade)
- 3) Lot Number or unique identification number
- 4) The Actual Analytical results obtained, i.e., 99.9% Nitrogen.
- 5) Supplier's signature and the date.

After the filling operations are completed, the **second valve leak test** should be performed. This test detects any valve outlet leaks. If any leaks are detected, the cylinder should be removed from service and quarantined until repairs can made.

TESTING AND RELEASE

Sections 211.165(a) & 165(e)

Due to the uniqueness of medical gases, each firm is required to determine the identity and strength of 1) the incoming drug product, and 2) the drug product delivered to a consignee, customer, or patient. Testing should be by appropriate methods to determine conformance with official specifications.

The testing requirement for cylinders filled on a multiple outlet manifold is one filled cylinder from each manifold filling sequence should be assayed for identity and strength, either by 1) the U.S.P. test procedure or 2) a validated test procedure capable of producing equivalent or greater than U.S.P. test results.

For high pressure cylinders filled individually, one filled cylinder per uninterrupted filling sequence

should be tested for identity, strength, and odor. An uninterrupted filling sequence is a single, continuous filling sequence with no breaks or shut-downs occurring during the filling provided the same personnel, equipment, and lot of component are used. If the filling sequence is interrupted then additional testing is required.

According to the U.S.P. an odor test is required to be performed on each high pressure cylinder tested. This odor test should not be confused with the odor test performed during the prefill operations, and is required to be recorded on either the batch production record or a separate testing log. An odor test should not be performed directly on any liquid due to the possibility of frostbite. However, an odor test should be performed on a vaporized sample of the liquid product obtained through the product withdrawal connection on the liquid vessel..

The testing requirements for cryogenic vessels have been addressed previously under Liquid to Liquid Filling, Items #1 - 3, and Liquid to Gas and Filling Large Cryogenic Vessels.

A word of caution, a firm cannot receive industrial grade product and simply perform the U.S.P. tests to convert it into a medical grade product, since you cannot test CGMP into the product, it must be present throughout the entire process. A firm must receive medical grade product in order to supply medical grade product. Medical grade product may be used for other applications, such as foods, beverages, even industrial uses, but cannot bear the U.S.P./NF designation.

What is the official method as outlined in the United States Pharmacopeia (U.S.P.) 23.

Oxygen Monograph

The U.S.P. oxygen monograph lists the potency as being not less than 99.0% by volume of O₂. It also states that oxygen produced by **the air liquefaction process** is exempt from the requirements of the test for *Carbon dioxide and Carbon monoxide*.

Note: If a firm fills Oxygen U.S.P. and fails to have a certificate of analysis on file documenting that the oxygen is produced by the air liquefaction process, or if the label lacks this statement, then a firm would be required to perform the additional contaminant testing for carbon dioxide and carbon monoxide tests, not just an identity and strength test.

The official method which is commonly referred to as the "ORSAT" buret method utilizes a calibrated 100 ml buret, copper wire, and ammonium chloride and ammonium hydroxide solutions which are mixed together and equilibrated by agitation with the copper wire. A 100.0 ml sample of the gas is drawn into the buret and agitated, the residual gas is then measured.

In addition, a specific identity test is required to be performed at the same time, since carbon dioxide is capable of giving similar results. This is usually accomplished by using either a carbon dioxide detector tube or a properly calibrated handheld oxygen analyzer.

The accuracy of the U.S.P. procedure is $\pm 0.1\%$.

The General Notices, Foreign Substances and Impurities states while one of the primary objectives of the Pharmacopeia is to assure the user of official articles of their identity, strength, quality, and purity, it is manifestly impossible to include in each monograph a test for every impurity, contaminant, or adulterant that might be present, including microbial contamination. These may arise from a change in the source of material or from a change in the processing, or may be introduced from extraneous sources. Tests suitable for detecting such occurrences, the presence of which is inconsistent with applicable manufacturing practice or good pharmaceutical practice, should be employed in addition to the tests provided in the individual monograph.

LIQUID PHASE

Because the pressure in a closed vessel containing carbon dioxide and nitrous oxide will increase with a rise in temperature, the possibility always exists that a cylinder filled at a safe pressure at normal temperatures might reach a dangerously high pressure at high ambient temperatures. Therefore, nitrous oxide and carbon dioxide are filled individually on a scale, as liquids where pressure does not indicate the amount filled. These cylinders are filled individually by weight which should not exceed 68% of the weight of water the cylinder will hold at 60°F (15.6°C).

One cylinder filled during an uninterrupted filling sequence should be tested for identity and strength, prior to release.

If a firm is utilizing the Pressure Differential method to assay nitrous oxide, please beware that an identity test is required to be performed concurrently, since carbon dioxide and nitrous oxide can mix. The pressure differential method has been evaluated and found to be an acceptable alternative testing methodology.

If a carbon dioxide identity test is not performed concurrently, then the analysis of the finished drug product is not acceptable.

GAS MIXTURES

If the product is a mixture of two gases, then every cylinder should be tested for the identity and strength of one of the gases, usually the active ingredient. In addition, an identity test for the other gas should be performed on one cylinder from the manifold filling sequence.

For a mixture containing three gases, every cylinder should be tested for the identity and strength of two of the gases, and one cylinder from each manifold filling sequence should be tested for the identity of the third gas.

Testing of Nitrogen NF

For firm's receiving shipments of Nitrogen NF, at the current time, all of the following criteria are required to be met. Once a firm has complied with the following, then the firm would not be required to utilize a gas chromatograph to assay the Nitrogen NF.

- 1) the supplier of the incoming nitrogen should be registered with FDA;
- 2) ***a valid certificate of analysis is received with each delivery of nitrogen, with the product being designated as Nitrogen NF;***
- 3) the filling system has dedicated lines, and these supply lines are traceable from the storage tank to the filling manifold. If there exists a possibility that another gas, whether it be industrial or medical could be introduced and contaminate the product, then in addition to full U.S.P. testing, a test for the absence of the contaminating gas would be required;
- 4) ***testing for the lack of oxygen, i.e., less than or equal to 1.0%. This may be accomplished with an oxygen analyzer having the capability of producing results between 0 - 1% and being properly validated against the U.S.P. methodology [See 211.165(e) below]. In addition, if using an acceptable paramagnetic oxygen analyzer, both the "zero and span" steps, are required to be performed with a calibration standard of high purity nitrogen, and a calibration standard with an oxygen concentration of less than or equal to 1.0%; and***
- 5) perform a supplier audit. If a firm's supplier forbids this requirement due to proprietary information, then a firm should receive a letter from the supplier attesting to this fact, and this letter should be maintained.

Alternative Analytical Equipment **Sections 211.165(e)**

If an alternate testing method, i.e., non-U.S.P. methodology is to be used for the analysis of medical gases, then the accuracy, sensitivity, and reproducibility of the method is required to be established and documented. This would include changes to the analytical methodology, such as a different column length, or a different carrier gas, etc.

In accordance with 211.165(e), each firm is required to maintain on file a copy of the actual validation study for each analyzer demonstrating U.S.P. equivalency. Further, the manufacturer's instruction manual must be on file to assure proper calibration of the analytical equipment.

In addition, USP23, Section 1225, page 1982, titled Validation of Compendial Methods should be used to perform any analytical testing methodology equivalency.

On the other hand, properly calibrated handheld oxygen analyzers provide a specific oxygen identification test result only, but are not suitable for U.S.P. assay testing. At the present time, we are unaware of any of these instruments that have the accuracy required to provide an equivalent Oxygen U.S.P. strength result. Typically, these analyzers have an accuracy of ± 1 to 3%, not the required $\pm 0.1\%$.

CAUTION: If you are using a handheld oxygen analyzer for the analysis of an oxygen concentrator output, please contact the analyzer manufacturer to determine if your oxygen analyzer may be used for identity testing of Oxygen U.S.P., i.e., greater than or equal to 99.0% oxygen. We have received reports that certain handheld analyzers may not be used for the identity testing of Oxygen U.S.P.

RECORDS & REPORTS

Section 211.180(a) & 182

Any record required by the CGMPs should be maintained in compliance with this part. This would include training records, certificates of analysis, equipment cleaning & calibration logs, label reconciliation logs, master production records, batch production records, analytical equipment calibration logs, testing records, complaints files, etc.

Record retention requirements:

- 1) if an expiration date is used, then all records should be retained for at least one (1) year after the expiration date of the batch, or
- 2) if no expiration date is used, then records should be retained for at least 3 years after distribution of the batch.

Records may be in the form of true copies or electronic copies. Records covering equipment cleaning and/or maintenance should be established. For the filling of cryogenic home vessels, there should be a separate log documenting when a vessel is sent out for maintenance or repair, and when the vessel has been assayed, prior to redistribution.

The Electronic Records and Electronic Signatures regulations [21 CFR Part 11] became effective on August 20, 1997; therefore, prior to converting your operation from paper to electronic records, you should be in compliance with these regulations.

MASTER PRODUCTION AND CONTROL RECORDS

Section 211.186

While master production and control records are required, this requirement may be met by

establishing a manual containing all written operating procedures, an actual specimen of each label applied to the drug product [This is commonly referred to as the approved master label], the date and signature of the individual responsible for the preparation of all required records, and the signature of a second person designated as the quality control individual who independently checked and dated these records.

BATCH PRODUCTION AND CONTROL RECORDS

Section 211.188

Batch production records should document all significant steps performed during the filling operations, such as the prefill inspections for the high pressure cylinders and cryogenic vessels, the number and size cylinders filled, the filling inspections, the post fill checks, analytical test results, the lot number assigned, the final temperature and pressure results, labeling accountability, i.e., issued, applied, returned, damaged, etc., the initials of the pumper/analyst, the signature of the individual who checked the entries for accuracy and completeness, the dates the above procedures were performed, etc.

Batch production records should be reviewed prior to the release of the finished drug product.

It is unacceptable to use a single entry to indicate that all of the significant steps have been performed, or to use a “✓” where the actual value is required to be recorded such as the temperature/pressure readings, purity and identity results, etc. A firm should amend its batch production record to provide for an item by item entry. [See the attached batch production record example for high pressure cylinder filling for details.]

A batch production record is a control record documenting that all of the required operations were performed during a comprehensive or elaborate manufacturing procedure or process. In fact, a batch production record is a snapshot of the actual production at the time of its performance, therefore, each significant steps should be documented as the operation is completed.

LABORATORY RECORDS

Section 211.194

Laboratory records should include complete data derived from all tests necessary to assure compliance with established specifications and standards. This would include all graphs, charts, etc., all calculations performed in connection with a test especially for mixtures or blends, the initials or signature of the analyst, and the initials or signature of a second individual showing that the original records have been reviewed and are in compliance with all established standards.

When using a handheld oxygen analyzer to perform an identity test, the actual results obtained must be recorded, i.e., 99.8%. A firm should establish written procedures addressing the

acceptable range which would be a factor of the accuracy of the analyzer. For example, if the oxygen analyzer has a 2.0% accuracy, then the range would be between 97.0% and 102.0%.

CERTIFICATE OF ANALYSIS (COA) - Incoming Supply

All incoming supplies of medical grade product should be accompanied by a COA containing at a minimum the following information:

- 1) Supplier's name and complete address
- 2) Name of the Product, i.e., Oxygen U.S.P.; Carbon Dioxide U.S.P.; Nitrogen NF; Nitrous Oxide U.S.P.; Helium U.S.P.; and Medical Air U.S.P.

NOTE: The following statement would not be acceptable, "Conforms to U.S.P./NF Requirements."

- 3) An Air Liquefaction Statement where appropriate
- 4) A Lot Number or other unique identification number
- 5) The Actual Analytical results for full U.S.P. monograph testing. [Please note that a statement indicating, "Meets the minimum purity of 99.5%, etc. is not acceptable."]
- 6) The Test Method used to perform the analysis. The statements "Meets U.S.P. specifications" is not acceptable, nor is "Tested via Servomex" since the specific model number is not provided
- 7) Supplier's signature and the date, and
- 8) If applicable, the signature of the employee witnessing the testing at the supplier.

DISTRIBUTION RECORDS

Section 211.196

Records should contain the name and strength of the product, what the patient received, i.e., D, E cylinders, cryogenic home vessel, etc., the name and address of the consignee, customer, or patient, and the date and quantity shipped.

A firm should establish a system whereby the distribution of each lot of a medical gas can be determined in the event that a recall becomes necessary. Please note that the distribution records for compressed medical gas products are not required to contain lot or control numbers in accordance with this section.

COMPLAINT FILES

Section 211.198

Written procedures should be established and followed describing the handling of all written and oral complaints, a detailed written record of each complaint, any investigation conducted, where an investigation is conducted, the written record shall include the findings of the investigation and follow-up, and documentation of the review by the quality control unit.

These procedures shall include provisions for review to determine whether the complaint represents a serious and unexpected adverse drug experience which is required to be reported to the FDA in accordance with Section 310.305.

Section 310.305 requires any person whose name appears on the label of a marketed prescription drug product as its manufacturer, packer, or distributor shall report to FDA each adverse drug experience received or otherwise obtained that is both serious and unexpected as soon as possible but within 15 working days of initial receipt of the information. This would include any problems associated with the drug product, the valve, the high pressure cylinder, etc.

In addition, according to Section 314.80, which became effective April 6, 1998, an Adverse Drug Experience Report must be filed for any adverse event associated with the use of a drug in humans, whether or not considered drug related, including: problems associated with the valve, a valve seal, i.e., Kel-F, ejection of valve stems, the container whether it be a high pressure cylinder or a cryogenic vessel, any deaths or injuries resulting from mix-ups, contaminations, etc., changing outlets which result in either death or injury, etc.

RETURNED DRUG PRODUCTS

Section 211.204

All returned high pressure cylinders are required to be vented to the atmosphere, even if the drug product has not been used, and the seal is intact. Under no circumstances, should the cylinders be redistributed to patients until all required prefill, fill, and post fill operations and finished product testing have been completed.

DRUG PRODUCT SALVAGING

Section 211.208

Products failing to meet U.S.P. specifications are required to be vented. Repeated testing, in order to pass a drug product is not allowed, unless a thorough investigation is performed, completed, documented, and reviewed by the quality control unit.

AIR SEPARATION PLANTS or UNITS

Air separation plants or units (ASU) take atmospheric air and through a purification process of cleaning, compressing, and cooling, separate the air into the constituent gases, oxygen, nitrogen, and argon. ASUs are highly computerized, and have very few employees in attendance during operations, which are usually 24 hours a day, 7 days a week. Therefore, process validation, and especially validation of computerized processes, is essential to ensure proper functioning of the process, and the product quality.

The requirement for computerized process validation has been around since the last major revisions to the current good manufacturing practice regulations which occurred on September 29, 1978. Process validation was addressed in FDA's 1987 Guideline on General Principles of Process Validation, and much has been written about this subject in the industry trade press. Therefore, both the requirements and the agency's expectations have been around for some time.

For unvalidated ASUs that have been in operation, i.e., shipping medical grade product, firms may apply, as a remedial measure, retrospective validation. (Product shipped from such unvalidated processes would be adulterated in the CGMP context.) As addressed in the 1987 validation guideline, a key principle in retrospective validation is that current operations are the same as past operations with respect to product specifications, the range of operating conditions, and equipment (ranges and changes). It is important that all changes and controls implemented since the original distribution of medical grade product in the retrospective period have been sufficiently documented. Otherwise, retrospective validation would not be scientifically sound, and older ASUs would need prospective validation, as would a new ASU that has not distributed medical grade product.

Process Validation as defined in the Guideline on General Principles of Process Validation, May 1987, is establishing documented evidence which provides a high degree of assurance a specific process will consistently produce a product meeting its pre-determined specifications and quality attributes.

The following CGMPs which have been previously discussed in detail are required:

- *process validation including computer systems validation*
- *establish a Quality Control Unit and written procedures*
- *training*
- *in process testing*
- *lot numbering*
- *written procedures*
- *calibration of analytical equipment*
- *testing finished product*
 - U.S.P. equivalent testing methodology*
 - testing residual, i.e., tankers, trailers, etc. prior to filling*

- *validation of non-U.S.P. testing methodology*
- *batch production records*
- *second person review of all pertinent records prior to release of the finished drug product especially during night time operations, when employees may not be present*
- *documentation*
- *certificate of analysis provided with each load, and all medical product designated as U.S.P./NF, if sold to a medical drug filler.*

HEALTH CARE FACILITIES INSTALLATIONS

In 1996, 11 tragic deaths occurred in a Temple, Texas hospital during the installation of an oxygen storage tank. The hose used to connect the temporary oxygen supply to the hospital's oxygen system was not purged of a toxic cleaning solution, and the installing firm failed to detect the toxic contaminant prior to its installation.

Health care facility installations usually occur at hospitals, nursing homes, clinics, etc. and usually involve the removal of the old supplier's storage tank and installation of a new storage tank.

FDA determined the industry was failing to comply with the CGMPs for this type of operation. During the July 1996, Compressed Gas Association (CGA) meeting, these requirements were discussed in detail. Further discussion occurred during the October 30, 1997, Clearwater CGA meeting, where specific CGMP requirements were outlined to assist the industry in achieving compliance.

Industry incorrectly assumed that compliance with the standards addressed in NFPA (National Fire Protection Association) 50, Standard for Bulk Oxygen Systems at Consumer Sites, and 99, Health Care Facilities were sufficient. However, under the NOTICE section of both NFPA 50 and 99 is the statement, "Users of this document should consult applicable federal, state, and local laws and regulations."

The CGMPs cover the entire initial installation operation and end at the point where the piping enters the building, and anytime the system is opened and exposed to a possible contaminant or impurity, such as new valve installation, new piping, etc. It is a firm's responsibility to determine the critical points and areas of their operation where problems or contamination may occur and to assure compliance with the following CGMPs which have been discussed in detail previously:

- *establish a Quality Control Unit and written procedures*
- *training of the service technicians, etc.*
- *qualifying equipment for medical use*
- *vendor/supplier audits of contracted cleaning firm(s) and written agreements*

- *written procedures*
- *calibration of testing analyzers*
- *finished product testing prior to introduction of the drug product into the hospital system*
- *U.S.P. equivalent testing methodology*
- *batch production records*
- *certificate of analysis provided to the receiving facility with each delivery*
- *documentation.*

If a supplier or shipper contracts with a third party to install a health care facility storage tank, it would be the supplier or shippers responsibility to determine that the system has been installed in accordance with the CGMPs and NFPA requirements, prior to introducing the medical gas. This determination should be fully documented.

Please note each installation is required to comply with both the CGMPs and the requirements outlined in NFPA 99 and 50, in order to assure proper installation.

CARBON DIOXIDE MANUFACTURERS & WHOLESALE DISTRIBUTORS

On January 2, 1998, we informed the industry that all carbon dioxide facilities that produce carbon dioxide are required to register and list by February 2, 1998. In addition, they should perform process validation including computer validation and comply with the CGMPs. It is essential that the firm have a written guarantee with the raw material manufacturer to be notified of any change to the production process or to the raw material. Another vital issue is the initial fingerprinting or characterization of the incoming "raw material" for any contaminants or impurities that could affect the finished drug product.

The following CGMPs which have been discussed previously in detail are required:

- *process validation including computer systems validation*
- *raw material supplier agreements*
- *raw material or stream fingerprinting or characterization*
- *establish a Quality Control Unit and written procedures*
- *training*
- *in process testing*
- *lot numbering*
- *written procedures*
- *calibration of analytical equipment*
- *testing finished product*
 - U.S.P. equivalent testing methodology*
 - testing residual, i.e., tankers, trailers, etc. prior to filling*
- *batch production records*
- *documentation.*

Finally, the product must be labeled either Carbon Dioxide U.S.P. or "For Industrial Use Only" or "Not for Human Drug Use." Once a carbon dioxide manufacturer has complied with all of the CGMPs and the process has been sufficient validated, the drug product may bear the "Carbon Dioxide U.S.P. designation only.

All shippers, wholesale distributors, transporters, etc. that fill into or from rail cars, storage tanks, trailers, vessels, etc. would be required to register and list and comply with the appropriate CGMPs.

LARGE CRYOGENIC VESSEL DELIVERIES TO HOSPITALS, ETC.

In the past 2 years, FDA has received reports of deaths and serious injuries occurring at 3 different hospitals around the country involving large cryogenic vessels. In each case, the invoice requested medical oxygen and the driver included with the delivery a vessel containing industrial grade product. In 2 of the cases, the industrial grade product was nitrogen, and in the third case the product was argon. In all three cases, the drivers failed to receive adequate CGMP training, in fact, one driver had failed the firm's driver certification test, and inadequate quarantine area on the trucks contributed to the mix-up.

In addition, the outlet fitting or connection on the industrial vessels were replaced with an oxygen outlet fitting or connection to allow connection with the hospital system.

Due to the imminent health hazard, FDA is moving rapidly to correct this practice in anticipation of preventing deaths or injuries from occurring in the future. Therefore, all large cryogenic vessels used for medical product should be dedicated to medical use only; should be equipped with either permanent non-removable fittings or connections, i.e., silver brazened, or some type of tamper-evident device on each fitting or connection, and should have a medical designation, i.e., Oxygen U.S.P. applied on the dome under each fitting or connection or a 360 degree wrap-around tape at the top of the vessel.

OXYGEN CONCENTRATORS

Oxygen concentrators require strict adherence to the manufacturer's recommended maintenance requirements to assure proper functioning of the unit, and to assure an adequate oxygen purity at the designated flow rates. Each unit contains several filters that require periodic monitoring, cleaning, and/or changing to assure proper functioning. Further, oxygen purity should be verified periodically whether the unit is in the patient's home or at the firm. The purity of the output should be determined at the indicated flow rates addressed in the manual, such as 96.0% at 2 liters per minute, or 93.0% at 6 LPM.

All required maintenance checks, oxygen analysis, etc. should be documented on an appropriate

oxygen concentrator log.

During an inspection, any problems pertaining to the performance characteristics of the device itself, are covered under the device CGMPs and should be discussed with the Center for Devices and Radiological Health's Office of Compliance. On the other hand, problems pertaining to the performance characteristics of or other claims regarding the oxygen flow itself, are covered under the drug CGMPs.

SPORTS OXYGEN

SPORTS OXYGEN is a small pocket-sized, personal use oxygen system, which has been imported from Japan. The product promises athletic enhancement and makes other drug claims. However, because these products are incapable of supplying an oxygen flow rate of at least six (6) liters of Oxygen U.S.P. per minute for at least 15 minutes, they are considered new drugs. Without an approved NDA, this product may not be legally imported into the U.S. and is covered under Import Alert 66-37.

ADAPTERS

The use of adapters to circumvent the specific CGA valves associated with a specific medical gas is not only illegal, but is also a very dangerous practice. There have been mixups and contamination that have occurred in the past due to the use of adapters which resulted in deaths and serious injury.

For the filling of mixtures, adapters may be used, however, written procedures detailing a system of checks should be in place to prevent mixups or contamination, and these should be documented. The adapters are required to be under security with limited access.

What are the possible consequences of not complying with the CGMPs?

How many times have you heard the statement, "What could go wrong with my oxygen? I buy it from a reputable source! I know what I'm doing! I fill oxygen only!"

Well, manufacturers report that each year there are returned to them supposedly empty cylinders that contain either a gas other than that originally shipped or a foreign odor. Some of these contaminating gases may be flammable, and intermixing a flammable and an oxidizing gas may cause a serious explosion.

On May 24, 1983, a large welding supply company in the southeast, delivered and connected a VGL thought to contain medical oxygen to a local hospital. During the course of the evening, the product was administered to a premature infant, a 46 year old male, and a 27 year old female in three different areas of the hospital and all three died. Analysis of the gas found that the alleged oxygen was in fact argon. To further complicate matters, the VGL was partially labeled "Liquid O" and had a second

label on the other side which read argon, and the fill line had an argon fitting while the discharge line had an oxygen fitting.

In 1987, a large welding supply company located in the northeast, jury-rigged four oxygen cylinders and placed CO₂ into these cylinders which were not painted the appropriate color for oxygen. However, the cylinders were correctly labeled as Oxygen U.S.P. and had the correct CGA 540 oxygen valve.

In addition, the firm failed to have written procedures covering the filling and handling of different colored cylinders. Four (4) of the cylinders were subsequently sent to a hospital and administered to two patients undergoing surgery. One patient's death was attributed to carbon dioxide exposure while the other patient was seriously injured.

On December 20, 1993, a home care company located in the northeast and filling liquid oxygen only, had its employee go to their supplier to pick up a GP-45 of Oxygen U.S.P. The supplier's employees were very busy and were unable to accompany the home care company's employee to the loading dock, so they authorized the employee to go to the loading dock and select one of the GP-45s. Unfortunately, the employee who was inadequately trained, selected a GP-45 of argon, not Oxygen U.S.P. Although a certificate of analysis was provided, no testing was performed and the labeling was not examined.

The employee loaded the vessel into the van and went to three (3) patients homes to fill their vessels, however, the employee encountered one little problem. When he went to fill the cryogenic home vessels, the discharge line was not compatible with the vessels fittings. So he took a fitting from a spare oxygen vessel and installed it on the GP-45, he could now fill the patients cryogenic vessels with the deadly product. Luckily, the next day, the employee became aware of the argon mixup and retrieved all 3 vessels with no injuries. Fortunately, these three patients were not dependent on high inspired oxygen concentrations.

In March 1996, we received a report of eleven deaths associated with contaminated oxygen being introduced at a VA hospital in the southwest. According to the report, a large storage tank was being replaced, and a temporary 500 gallon cryogenic vessel was brought in and connected to the hospital's main oxygen system via a 50 foot hose. A subsequent analysis of the 50 foot hose tested positive for the presence of trichloroethylene, a standard cleaning chemical.

On July 15, 1996, in Fredericksburg, Virginia, the former president of a medical oxygen facility pleaded guilty to making false statements to the Food and Drug Administration about his company's testing and filling of medical oxygen. During the February inspection, the president was informed of significant CGMP violations occurring at the firm. In March, he agreed to recall the adulterated drug product and informed FDA that he had done so. However, FDA later discovered that the firm in fact did not recall the adulterated product. The president was sentenced to serve one year and one day in prison, to perform 200 hours of community service, and to pay a \$30,000 fine for making false statements to FDA.

On December 2, 1996, a children's home located in New York reported adverse reactions experienced by nine patients due to the inhalation of carbon dioxide, instead of oxygen. Our investigation found the firm supplying the medical grade product had delivered a cryogenic vessel of industrial grade carbon dioxide which was properly labeled. An employee of the home went to attach a cryogenic vessel of Oxygen U.S.P. and inadvertently selected the carbon dioxide vessel and failed to notice the label. He noted the fittings on the carbon dioxide vessel weren't compatible with the connector on their oxygen system, so he removed an oxygen fitting from an empty vessel and installed it on the carbon dioxide vessel. He then introduced the carbon dioxide into the oxygen system. Two of the patients were injured critically, four experienced varying stages of respiratory distress, and three were not affected. In addition, the deliver driver had received no training in the CGMPs, and the truck had inadequate quarantine areas for medical and industrial grade product.

In October 1997, we received a report of a death occurring at a hospital located in Nebraska due to the inhalation of argon. The hospital received a shipment of Oxygen U.S.P. in cryogenic vessels, including one cryogenic vessel of argon which was properly labeled. The hospital was running low on oxygen and sent a maintenance man to connect a new oxygen supply vessel to their system. He selected the argon vessel, failed to notice the argon label and was unable to connect the vessel to the oxygen system. He removed the fitting from an empty oxygen vessel, installed it on the argon vessel, and was then able to connect the deadly product to the oxygen system. Argon was administered to a patient who was undergoing minor surgery, and this patient died. Once again, the delivery driver was not adequately trained on the CGMPs, and the truck had inadequate quarantine areas for medical and industrial grade product.

On April 22, 1998, a hospital located in Idaho discovered a large cryogenic vessel of industrial nitrogen had been connected by the supply firm's driver to their oxygen system which supplied the operating rooms, labor and delivery rooms, and the emergency room. The delivery driver was an inadequately trained college student who had failed the firm's required driver certification test. When the driver was unable to connect the incompatible nitrogen vessel outlet fitting, he obtained a crescent wrench, disconnected the nitrogen fitting and replaced it with the appropriate oxygen fitting so that it could be connected to the system. Unfortunately, two deaths are associated with the administration of the toxic industrial product.

Please note all of the above three incidences were in violation of industry practice and the CGMPs.

What's on the horizon for medical gases:

- *official guidance for medical gases;
- *final decisions on the CGA citizen petition regarding expiration dating and stability studies;
- *final labeling guidance for all medical gases.

GLOSSARY

The following definitions are provided to assist the reader in using this document.

1) **Cascading** - This is a cylinder filling system consisting of several large sized cylinders, such as H or K-sized cylinders as the supply source or commonly referred to as a "Bank" and a filling manifold capable of filling smaller cylinders, usually D or E cylinders, either one at a time or multiple cylinders. The first supply cylinder's valve is opened and the gas flows into the smaller cylinder(s) until equilibrium is reached. When this occurs, the first cylinder's valve will be closed and the second supply cylinder's valve will be opened allowing the gas to flow into the smaller cylinder(s). This continues until the smaller cylinder(s) is filled.

2) **Certificate of Analysis** (COA) is a single document required to be provided with every shipment of a drug product that in turn will undergo further processing, i.e., filling, transfilling, etc. The COA should contain all of the required information that would allow the receiving firm to determine if the drug product is acceptable. This document may come in any form, such as a letter of conformance, a bill of lading, an invoice, etc. and does not have to be identified as a "COA" but must contain all of the required information. Otherwise, it would be deemed unacceptable and further testing may be required.

3) **Cryogenic home vessels** (CHV) are vessels designed to hold liquid oxygen at a patient's home.

4) **Distributor** is a firm that receives fully labeled, finished drug product either liquid in large cryogenic vessels, i.e., VGLs/GPs, etc. and/or high pressure cylinders and does not manipulate the product nor the labeling in anyway. Therefore, they are not required to register.

However, a distributor should establish and follow recall, complaint and distribution procedures capable of determining the traceability of the drug product.

5) **Handheld oxygen analyzers** are oxygen analyzers which may be held in ones hand or may be stationary, that operate on the fuel, electrochemical, galvanic, or polarographic cell principle. When properly calibrated, these analyzers may provide a specific oxygen identification test result only, since they fail to possess the required U.S.P. accuracy.

A note of caution: If you are using a handheld oxygen analyzers intended for analysis of the oxygen concentrator output, please contact your oxygen analyzer manufacturer to determine if your oxygen analyzer may be used for identity testing of Oxygen U.S.P., i.e., greater than or equal to 99.0% oxygen.

6) **Home Care Company/Home Respiratory Care Company (HCC)** are usually sell durable medical equipment and supply liquid oxygen to patients are their home. These firms may also fill via cascading high pressure cylinders

7) **Large cryogenic vessels or Dewars** are containers used to hold a low pressure, liquid product which is at a very low temperature, and are similar in design to that of an insulated thermos bottle with a vacuum between the inner and outer container. These vessels contain the incoming drug product, and may be either permanently mounted in a vehicle, such as HL119s, MDX 60s, 80s, 119s, etc., or may be portable such as VGLs (Vertical Gas Liquid), GPs (Gas Pack), or PLCs (Portable Liquid Container). This does not pertain to tankers, etc.

8) **Manufacturer** is any person or firm filling liquid to liquid, liquid to gas, and/or gas to gas. As a manufacturer you are required to register and list with the agency and to comply with the CGMPs. In addition, you should check with your state to determine if there are any state requirements, such as licensing that you may need to comply with.

*9) **Oxygen for Environmental Use** means oxygen meeting the U.S.P. specifications and used to support life artificially in environments which are normally deficient. This definition includes, but is not limited to, space and space simulation capsules, deep submersibles, scuba, etc. It specifically excludes oxygen used in chambers or devices for the medical therapeutic treatment of man or animal.*

*10) **Oxygen for Industrial Use** means oxygen not intended for inhalation or therapeutic treatment of man or animal.*

*11) **Oxygen for Aircraft Use** means oxygen in fixed or portable oxygen containers or systems intended for commercial or private aircraft use, meeting the U.S.P. specifications and having the special moisture and/or other limiting characteristics required for aviators breathing oxygen (ABO). ABO may not be used for medical therapeutic treatment of man or animal.*

12) **Storage Tank or Stand Tank** is a large cryogenic stationary holding tank with a capacity of several thousand gallons/liters of a liquid product. These are located on the outside a facility.

13) **Uninterrupted filling sequence** is a single, continuous filling sequence with no breaks or shut-downs occurring during the filling and provided the same personnel, equipment, and lot of component are used. If the filling sequence is interrupted then additional testing is required.

This procedure does not apply to the filling of high pressure cylinders on a multiple outlet manifold or rack.

14) **United States Pharmacopeia 23/National Formulary** (U.S.P./NF) is a reference of a select list of articles in the form of a monograph. Included in each monograph are the standards for determining the identity, strength, quality, and purity of the articles. Please note each individual monograph does not contain all contaminants or impurities that may be present. Refer to the General Notices under U.S.P. Monograph for details.